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Learning and Memory Enhancement by Neuropeptide
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The goal of this research is to discover mechanisms of cognitive enhancement in normal and impaired subjects. A major thrust of this work, is to study effects of the organometal neurotoxin trimethyltin (TMT) on learning in our autoshaping model, in which rats learn to touch a lever to obtain food. Trialkyltins are used as stabilizers for plastics, or as biocides for control of fungus, barnacles, bacteria and insects. Their toxic effects have been known for over 100 years (1). However, the specific neurotoxic effects of TMT were first observed after accidental exposure of two French chemical workers who experienceed memory loss and seizures (2). Since then, numerous investigations in rodents have confirmed that TMT, administered systemically, produces a relatively specific lesion in hippocampus and related olfactory cortical structures (3). These lesions are associated with impairments in learning and memory as measured in a wide variety of tasks (4). Thus, as well as being an environmental anti-fouling toxicant of specific interest to the Navy, the compound may also be of interest as a model treatment for study of learning/memory dysfunction.

During the past 6 months we have completed an initial dose-response study of effects of TMT on autoshaping and have submitted a paper for publication (C.A. Cohen, R.B. Messing and S.B. Sparber, "Selective Learning Impairment of Delayed Reinforcement Autoshaped Behavior Caused by Low Doses of Trimethyltin: No Evidence of Storage or Retrieval Deficits"). This study separates "non-specific" behavioral changes which may affect behavior of toxicant-exposed rats in assays of learning or memory from specific cognitive effects of the compound. In particular, TMT does not impair performance of easy versions of the autoshaping task with identical sensorimotor and motivational requirements, but when a delay of reinforcement of 6 sec is imposed rats given all three doses (3, 6 or 7.5 mg/kg of TMT) show impaired performance. However, the high dose rats show hyperreactivity and perseverative behavior (similarly to rats with large conventional lesions of the hippocampus), and actually manipulate the lever more than rats given lower doses. These high dose rats fail to learn a latent inhibition paradigm, also similarly to rats with large hippocampal lesions. The results thus suggest that the cognitive impairment may be separable from hyperreactivity and perseveration, since the latter effects only emerge at the high dose. Our low dose rats appear to be similar to normally aged rats, since they learn a task analagous to a classical conditioning delay paradigm, but cannot learn a trace paradigm (5). We have previously shown that rats treated with TMT have increased concentrations of forebrain ß-adrenergic receptors, and have hypothesized that these rats may have a deficiency of forebrain norepinephrine release similar to that seen with aged animals (6).

Also within the past 6 months, we have completed studies showing that rats treated with TMT or a mixed ganglioside preparation (which was administered to determine a possible therapeutic effect in TMT-treated animals) have decreased concentrations of hippocampal glucocorticoid receptors, which may be related to cognitive impairments. This is another parallel between these animals and aged rats which have deficiencies in this receptor (7). Complete manuscripts for this work are in preparation, but some of the work will be presented at the Xth International Congress of Pharmacology in August (S.B. Sparber, G. Seran, R.B. Messing, J.O'Callaghan and B. Berra, "Toxicity of mixed gangliosides (GS): Learning and Hippocampal Corticosterone Receptors"). Interestingly, TMT-treated rats have elevated levels of glial fibrillary acidic protein (GFAP), an indication of the cytotoxicity produced by this compound. Rats treated with gangliosides, which induce a cognitive impairment but no cell death, have normal levels of GFAP, but still exhibit the decrease in corticosteroid binding. Thus, this decrease is probably independent of hippocampal cell death, and may be a down regulation. In future work we wish to examine the effects of manipulations of the pituitary adrenal axis on TMT toxicity as measured behaviorally, biochemically and histologically.

We have also completed and submitted for publication a study of the effects of the α_2-noradrenergic receptor antagonist yohimbine on autoshaping (M.S. Huang, R.B. Messing and S.B. Sparber, "Learning Enhancement and Behavioral Arousal Induced by an Anxiogenic Drug"). This prototypical anxiogenic agent, which increases forebrain norepinephrine release, enhances

autoshaping in low doses, as does the putative learning/memory enhancing peptide, des-glycinamide arginine-8-vasopressin (DGAVP), as demonstrated in previous work (8-10). However, unlike DGAVP, yohimbine also induces increased behavioral arousal, which may account for its effects on autoshaping. In view of the altered norepinephrine receptor binding in forebrain of TMT-treated rats, we plan to test yohimbine and related compounds in rats treated with TMT. Within the last 6 months we have completed studies showing that DGAVP attenuates the learning impairment in TMT-treated animals, and that TMT induces a specific learning deficit without a retrieval deficit: rats which have already learned the autoshaping task and given TMT continue to perform. The manuscript describing this work is in preparation.

Finally, we have demonstrated that autoshaping is highly dependent upon the deprivation state of the animal: more food deprived rats learn faster. This is not simply a generalized behavioral activitation produced by food deprivation, since more food deprived rats also show better learning of latent inhibiiton. The manuscript describing this work is also in preparation. Our present research plans include studies investigating interactions between deprivation levels and effects of drugs and toxicants.

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